HEPATITIS C (HCV)/HIV COINFECTION (Updated December 1, 2009)

Long-term studies of patients with chronic hepatitis C virus (HCV) infection show that approximately 33% of the patients progress to cirrhosis at a median time of less than 20 years *[1-2]*. This rate of progression increases with older age, alcoholism, male sex, and HIV infection *[3-6]*. A meta-analysis demonstrated that the rate of progression to cirrhosis for persons coinfected with HCV/HIV was about three times higher than the rate for HCV mono-infected patients *[5]*. This accelerated rate is magnified in patients with low CD4 counts. Chronic HCV infection also complicates HIV treatment due to the increased frequency of antiretroviral (ARV)-associated hepatotoxicity *[7-8]*. Multiple studies have shown poor prognosis for HCV/HIV coinfection in the era of combination antiretroviral therapy (ART). It is unclear if HCV infection accelerates the rate of HIV progression *[9]* or if the accelerated rate primarily reflects the impact of injection drug use, which is strongly linked to HCV infection *[10-11]*. Although whether ART reduces the attributable morbidity/mortality from untreated HCV is unknown, the presence of chronic HCV infection influences the treatment of HIV with ARV as discussed below.

Assessment of HCV/HIV Coinfection Prior to Antiretroviral Therapy

- Prior to initiation of ART, HIV-infected patients should be screened for HCV infection with sensitive immunoassays licensed for detection of antibody to HCV in blood. To confirm the presence of chronic infection, HCV-seropositive persons should be tested for HCV RNA using a qualitative or quantitative assay *[12]*.
- Patients with HCV/HIV coinfection should be advised to avoid alcohol consumption, use appropriate precautions to prevent transmission of both viruses to others, and receive hepatitis A (HAV) and hepatitis B (HBV) vaccines if susceptible.
- All patients with HCV/HIV coinfection should be evaluated for HCV therapy. HCV treatment is recommended according to standard guidelines with strong preference for treating patients with higher CD4 counts. For patients with lower CD4 counts (<200 cells/mm^3), it may be preferable to initiate ART and delay HCV therapy until CD4 counts increase as a result of HIV treatment *[12-15]*.
- Concurrent treatment of both HIV and HCV is feasible but may be complicated by pill burden, drug toxicities, and drug interactions. Some notable considerations include:
    - Didanosine (ddI) should not be given with ribavirin because of the potential for drug-drug interactions leading to life-threatening ddI-associated mitochondrial toxicity including hepatomegaly/steatosis, pancreatitis, and lactic acidosis *[16]*.
    - Zidovudine (ZDV) combined with ribavirin should be avoided when possible because the higher rates of anemia associated with the combination make ribavirin dose reduction necessary *[17]*.
    - Abacavir (ABC) has been associated with decreased response to peginterferon plus ribavirin in some, but not all, retrospective studies; current evidence is insufficient to recommend avoiding this combination *[18-20]*.
    - Growth factors (e.g., filgrastim and erythropoietin) may be required to manage interferon-associated neutropenia and ribavirin-associated anemia; ZDV may increase the need for adjuvant growth factors due to increased bone marrow suppression *[17]*.

Antiretroviral Therapy in HCV/HIV Coinfection

- Hepatotoxicity: Drug-induced liver injury (DILI) following ART is more common in HIV/HCV coinfection. The greatest risk of DILI may be observed in coinfected persons with advanced liver disease (e.g., cirrhosis or end-stage liver disease) *[21]*. Eradication of HCV infection may decrease the likelihood of ARV-associated DILI *[22]*.
    - Given the substantial heterogeneity in patient populations and drug regimens, comparison of DILI incidence rates for individual ARV agents across clinical trials is difficult. In such studies, the highest incidence rates of Grade 3 or 4 elevations in liver enzyme levels have been observed during therapy with ARV drugs that are no longer commonly used in clinical practice and that include stavudine (d4T) (with or without ddI), nevirapine (NVP), full-dose ritonavir (RTV) (600 mg twice daily), or tipranavir (TPV) (boosted by low-dose RTV) *[23]*. Also, due to the potential for concurrent fatty liver disease (steatosis), the use of d4T or ddI should be limited *[24]*.
    - Patients should be monitored by following alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels at 1 month and then every 3 months after initiation of ART. Mild to moderate fluctuations in ALT and/or AST are typical in persons with chronic HCV infection. In the

absence of signs and/or symptoms of liver disease these fluctuations do not require interruption of ART. Significant ALT and/or AST elevation (>5 times the upper limit of the laboratory reference range) should prompt careful evaluation for signs and symptoms of liver insufficiency and for alternative causes of liver injury (e.g., acute HAV or HBV infection, hepatobiliary disease, or alcoholic hepatitis); short-term interruption of ART may be required *[25]*.

- When to start ART: The rate of liver disease (fibrosis) progression is accelerated by HIV/HCV coinfection, particularly in persons with low CD4 counts (≤350 cells/mm^3). Data derived largely from retrospective cohort studies regarding the effect of ART on the natural history of HCV disease are inconsistent *[6, 26-27]*. However, ART may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation *[28-30]*. Thus, for most coinfected patients including those with cirrhosis, the potential benefits of ART outweigh concerns regarding DILI.
    - ART should be started in HCV/HIV-coinfected persons in accordance with the Panel's recommendation for initiating ART in ART-naïve patients.

- What to start and what not to use: Initial combination regimens for the ARV-naïve patient with HCV/HIV are the same as for persons without HCV infection. HCV infection does not significantly alter the virologic or immunologic response to effective ART *[31]*. Special considerations for ART in persons with HCV/HIV coinfection include:
    - Patients receiving or considering therapy with ribavirin should avoid ddI, d4T, and ZDV.
    - ARV agents with the greatest risk of DILI should be used with caution.
    - Cirrhotic patients should be carefully assessed for signs of liver decompensation according to the Child-Turcotte-Pugh classification system because hepatically metabolized ARV drugs may require dose modification or avoidance in patients with Child-Pugh class B and C disease. (See **Appendix B, Table 7**.)

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